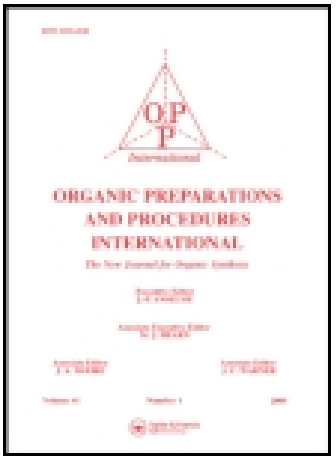

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Solvent-free Synthesis of 2,4,6-Triarylpyridine Derivatives Promoted by 1,3-Dibromo-5,5-dimethylhydantoin

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OPPI BRIEF

Solvent-free Synthesis of 2,4,6-Triarylpyridine Derivatives Promoted by 1,3-Dibromo-5,5-dimethylhydantoin

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The development of new methods for the synthesis of 2,4,6-triarylpyridines is an important area of research because of the broad spectrum of their biological and pharmaceutical properties such as anti-covulsant, anesthetic, anti-malarial, vasodilator, anti-epileptic character and their use as pesticidial, fungicidal and herbicidal agro-chemicals.[1–3] Due to their π-stacking ability, some pyridines are used in supramolecular chemistry.[4–7] The 2,4,6-triarylpyridine nucleus is structurally related to symmetrical triarylthio-, triarylseleno- and triaryltelluoropyrylium salt photosensitizers and has been recommended for photodynamic cell–specific cancer therapy.[8]

This wide range of applications has elicited several methods for their prepa-ration.[9–22] Among these, the one-pot reaction of aromatic ketones or aldehydes with ammonium acetate is one of the simplest and most straightforward approaches. A variety of reagents such as PEG-400,[23] $HClO_4.SiO_2$,[24] $H_{14}[NaP_5W_{30}O_{110}]$,[25] molecular iodine,[26] microwave irradiation without catalyst,[27] [BmIm][BF4],[28] wet 2,4,6-trichloro-1,3,5-triazine (TCT),[29] pentafluorophenylammonium triflate,[30] trichloroisocyanuric acid,[31] bismuth triflate,[32] and $MgAl_2O_4$ nanocrystals[33] have been employed to promote this transformation. Some of these procedures involve the use of strong corrosive acids or bases, solvents, microwave irradiation, metal salts, high catalyst loading and tedious work-up. Thus the development of a new readily available method that avoids many of these problems is highly desirable.

In recent years, 1,3-dibromo-5,5-dimethylhydantoin (*DBH*) has been used as a cata-lyst for a number of reactions[34–43] because it is relatively inexpensive, non-toxic, quite stable and easy to handle. We now report the preparation of 2,4,6-triarylpyridines from aldehydes and acetophenones by treatment with ammonium acetate in the presence of catalytic amounts of 1,3-dibromo-5,5- DBH under solvent-free conditions (*Scheme 1*).

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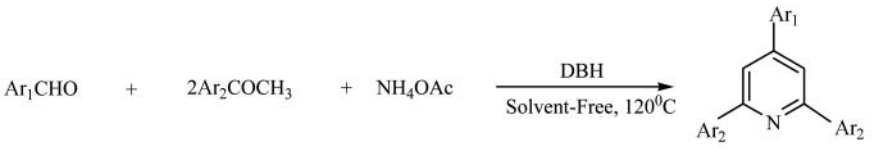

a) $Ar_1 = Ar_2 = C_6H_5$ **b)** $Ar_1 = 4\text{-}ClC_6H_4$, $Ar_2 = C_6H_5$ **c)** $Ar_1 = C_6H_5$, $Ar_2 = 4\text{-}MeC_6H_4$ **d)** $Ar_1 = 4\text{-}HOC_6H_4$, $Ar_2 = C_6H_5$ **e)** $Ar_1 = 4\text{-}(Me_2N)C_6H_4$, $Ar_2 = C_6H_5$ **f)** $Ar_1 = 4\text{-}MeC_6H_4$, $Ar_2 = 4\text{-}MeC_6H_4$ **g)** $Ar_1 = 2\text{-}MeC_6H_4$, $Ar_2 = C_6H_5$ **h)** $Ar_1 = 4\text{-}MeOC6H4$, $Ar_2 = 4\text{-}MeC_6H_4$ **i)** $Ar_1 = 4\text{-}ClC_6H_4$, $Ar_2 = 4\text{-}MeC_6H_4$ **j)** $Ar_1 = 4\text{-}ClC_6H_4$, $Ar_2 = 4\text{-}MeOC_6H_4$ **k)** $Ar_1 = 4\text{-}MeOC_6H_4$, $Ar_2 = 4\text{-}ClC_6H_4$ **l)** $Ar_1 = 4\text{-}MeOC_6H_4$, $Ar_2 = C_6H_5$ **m)** $Ar_1 = 2\text{-}ClC_6H_4$, $Ar_2 = C_6H_5$ **n)** $Ar_1 = 4\text{-}BrC_6H_4$, $Ar_2 = C_6H_5$ **o)** $Ar_1 = 4\text{-}NO_2C_6H_4$, $Ar_2 = C_6H_5$ **p)** $Ar_1 = 4\text{-}NO_2C_6H_4$, $Ar_2 = 4\text{-}FC_6H_4$ **q)** $Ar_1 = 4\text{-}CNC_6H_4$, $Ar_2 = 4\text{-}FC_6H_4$ **r)** $Ar_1 = 4\text{-}BrC_6H_4$, $Ar_2 = 4\text{-}FC_6H_4$ **s)** $Ar_1 = 2\text{-Furyl}$, $Ar_2 = C_6H_5$ **t)** $Ar_1 = 2\text{-Thienyl}$, $Ar_2 = C_6H_5$

Scheme 1 (Color figure available online.)

We initially examined the condensation of acetophenone (2 mmol), benzaldehyde (1 mmol) with ammonium acetate (2 mmol) in the presence of 10 mol% (0.1 mmol of DBH at 120°C under solvent-free conditions. The reaction proceeded rapidly to afford 2,4,6-triphenylpyridine (**3a**) in high yields (*Table 1, Entry 1*). Although a lower catalyst loading led to decreased yields (*Entry 2*), an increase of the catalyst loading did not improve the yield (*Entry 3*). A better yield of **3a** in a shortened reaction time was obtained at 100–120°C (*Entries 1, 4–5*) while the yield unexpectedly decreased to 64% with formation of dark material at 130° C (*Entry 6*) possibly due to the decomposition of the starting compounds or of the product. Thus, all reactions were performed at 120° C in the presence of 10 mol% of DBH (*Table 2*). In the absence of the catalyst, no product could be detected even after 7h (*Table 1*, *Entry 7*). The efficiency of various *N*-halo compounds was tested under the same conditions. Although NBS, *N*-chloro-succinimide (NCS) and 1,3-dichloro-5,5-dimethylhydantion (DCH) (*Entries 8–10)* gave nearly similar yields of

Table 1
Optimization Process

Entry	Catalyst (mol %)	Tem. (°C)	Time (h)	Yield (%)
1	10	120	3.0	90
2	5	120	4.5	72
3	15	120	3.5	83
4	10	110	4.5	60
5	10	100	6.0	52
6	10	130	3.5	64
7	none	120	6.0	traces
8	10[a]	120	3.5	88
9	10[b]	120	3.5	76
10	10[c]	120	3.5	84

[a]NBS used in reaction condition; [b]NCS used in reaction condition; [c]DCH used in reaction condition.

Table 2
One-pot Synthesis of 2,4,6-Triarylpyridines using 1,3-Dibromo-5,5-dimethylhydantoin (DBH)

	2,4,6-Triarylpyridines			mp (°C)	
Entry	**3a–t**	Yield (%)	Time (h)	Found	Lit.
1	**3a**	90	3	130–132	132–134
2	**3b**	86	3.5	123–125	120–122
3	**3c**	80	4	156–157	153–155
4	**3d**	76	4	189–190	190–193
5	**3e**	87	3	138–140	136–138
6	**3f**	90	4	177–179	178–179
7	**3g**	83	3.5	122–123	119–120
8	**3h**	86	3.5	153–155	152–154
9	**3i**	83	4	201–202	198–200
10	**3j**	88	3	113–115	112–114
11	**3k**	92	3	192–194	190–191
12	**3l**	90	3	101–102	99–100
13	**3m**	80	3.5	113–115	114–116
14	**3n**	89	4	165–167	164–166
15	**3o**	90	2.5	199–201	196–198
16	**3p**	92	3	251–253	248–250
17	**3q**	91	3	226–228	228–230
18	**3r**	84	3.5	195–196	192–194
19	**3s**	78	5	166–168	164–165
20	**3t**	82	4	170–172	172–174

3a (*Entries 8–10*, *Table 1*), the low cost, ready availability and stability of DBH recommend it as the preferred catalyst for this transformation.

Once these conditions were optimized, the generality of the reaction was examined with other substrates, using several aromatic aldehydes and ketones in the presence of 10 mol% (0.1 mmol of DBH) at 120°C under solvent-free conditions. The results are listed in *Table 2*. The condensation of benzalacetophenone – a possible intermediate – and 4-methoxyacetophenone with ammonium acetate in the presence of DBH under the same conditions proceeded smoothly in a shorter time (2.5 h) to give the expected product albeit in lower yield (74%). Treatment of propiophenone and butyro-phenone with benzaldehyde under similar conditions failed to give any product. All these reagents generate halonium ions that can activate the carbonyl groups of the aldehyde toward nucleophilic attack and promote enolization of the ketone as has been shown previously in the literature.[23–32]

We have also examined the recyclability of DBH. After the completion of the preparation of **3a**, hot EtOH (96%, 1 ml) was added and the solid catalyst separated by filtration. It was then washed with cold carbon tetrachloride and dried at room temperature for 20 h. Only marginal decreases in the yield of the product **3a** were observed in the first three runs (90, 86, and 82%, respectively) with recycled DBH.

In conclusion, we have described an efficient methodology for the synthesis of 2,4,6-triarylpyridines under solvent-free conditions. Simple procedures, high yields, easy

work-up, the avoidance of organic solvents and toxic reagents are significant advantages of the present method compared to the previous ones. Furthermore, DBH is relatively inexpensive and stable to air and moisture.

Experimental Section

All reagents and chemicals were purchased from Aldrich, Merck and Fluka and were used without further purification. IR spectra as KBr pellets were recorded on a Shimadzu 435-U-04 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained using Bruker DRX-300 Avance spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal reference. Melting points were determined in open capillary tubes in a Stuart BI Branstead Electrothermal Cat No:IA9200 apparatus and uncorrected.

General Procedure for the Synthesis of 2,4,6-Triarylpyridines.

DBH (10 mol %) was added to a mixture of the aldehyde (1 mmol), acetophenone (2 mmol), and ammonium acetate (0.154 g, 2 mmol) in a 10 mL flask at room temperature. The temperature was then raised to 120°C and maintained for the appropriate time (see Table 2) with stirring. After the completion of the reaction as indicated by TLC (hexane-ethyl acetate, 4:1), hot EtOH (96%, 1 ml) was added and the mixture stirred for 5 min. Then the catalyst was filtered off and the filtrate was poured into crushed ice. The solid product, which separated, was collected and recrystallized from ethanol (96%, 3 ml) to afford the pure 2,4,6-triarylpyridine **(3a-t)**.

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References

1. B. Y. Kim, J. B. Ahn, H. W. Lee, S. K. Kang, J. H. Lee, J. S. Shin, S. K. Ahn, C. I. Hong and S. S. Yoon, *Eur. J. Med. Chem.*, **39**, 433 (2004).
2. I. S. Enyedy, S. Sakamuri, W. A. Zaman, K. M. Johnson and S. Wang, *Bioorg. Med. Chem. Lett.*, **13**, 513 (2003).
3. A. D. Pillai, P. D. Rathod, P. X. Franklin, M. Patel, M. Nivsarkar, K. K. Vasu, H. Padh and V. Sudarsanam, *Biochem. Biophys. Commun.*, **301**, 183 (2003).
4. G. W. V. Cave, M. J. Hardie, B. A. Roberts and C. L. Raston, *Eur. J. Org. Chem.*, 3227 (2001).
5. R. K. R. Jetti, A. Nagia, F. Xue and T. C. W. Mak, *Chem. Commun.*, 919 (**2001**).
6. Z. C. Watson, N. Bampos and J. K. M. Sanders, *New. J. Chem.*, 1135 (**1998**).
7. E. C. Constable, C. E. Housecroft, M. Neuburger, D. Phillips, P. R. Raitby , E. Schofield, E. Sparr, D. A. Tocher, M. Zehnder and Y. Zimmermann, *J. Chem. Soc. Dalton Trans*, 2219 (**2000**).
8. K. A. Leonard, M. I. Nelen, T. P. Simard, S. R. S. O. Darvies, A. R. Gollnickoseroff, S. L. Gibson, R. Hilf, L. B. Chen and M. R. Detty, *J. Med. Chem.*, **42**, 3593 (1999).
9. F. Chubb, A. S. Hay and R. B. Sandin, *J. Am. Chem. Soc.*, **75**, 6042 (1953).

10. R. L. Frank and R. P. Seven, *J. Am. Chem. Soc.*, **71**, 2629 (1949).
11. F. Krohnke and W. Zecher, *Angew. Chem. Int. Ed.* **1**, 626 (1963).
12. F. Krohnke, *Synthesis*, 1 (**1976**).
13. K. T. Potts, M. J. Cipullo, P. Ralli and G. Theodoridis, *J. Am. Chem. Soc.*, **103**, 3585 (1981).
14. T. Kobayashi, H. Kakiuchi and H. Kato, *Bull. Chem. Soc. Jpn*, **64**, 392 (1991).
15. F. Palacios, A. M. O. de Retana and J. Oyarzabal, *Tetrahedron lett.*, **37**, 4577 (1996).
16. F. Al-Omran, N. Al-Awadi, A. A. El-Khair and M. A. Elnagdi, *Org. Prep. Proced. Int.*, **29**, 285 (1997).
17. A. Kumar, S. Koul, T. K. Razdan and K. K. Kapoor, *Tetrahedron lett.*, **47**, 837 (2006).
18. M. Adib, H. Tahermansouri, S. Aali Koloogani, B. Mohammadi and H. R. Bijanzadeh, *Tetrahedron Lett.*, **47**, 5957 (2006).
19. J. B. Hendrickson and J. Wang, *Org. Prep. Proced. Int.*, **35**, 623 (2003).
20. I. Eryazici, C. N. Moorefield, S. Durmus and G. R. Newkome. *J. Org. Chem.*, **71**, 1009 (2006).
21. M. Borthakur, M. Dutta, S. Gogoi and R. C. Boruah, *Synlett*, 3125 (**2008**).
22. G. W. V. Care and C. L. Raston, *Chem. Commun.*, 2199 (**2000**).
23. X. Ltuanj, H. X. Li, J. X. Wang and X. F. Jia, *Chin. Chem. Lett.*, **16**, 607 (2005); 143, 248227q (2006).
24. L. Nagarapu, A. R. Peddiraju and S. Apuri, *Catal. Commun.*, **8**, 1973 (2007).
25. M. M. Heravi, K. Bakhtiari, Z. Paroogheha and F. F. Bamoharram, *Catal. Commun.*, **8**, 1991 (2007).
26. Y. M. Ren and C. Cai, *Monatsh. Chem.*, **140**, 49 (2009).
27. S. Tu, T. Li, F. Shi, F. Fang, S. Zhu, X. Wei and Z. Zong, *Chem. Lett.*, **34**, 732 (2005).
28. H. Wu, Y. Wan and L. Lu, *Australian J. Chem.*, **12**, 155 (2009).
29. B. Maleki, D. Azarifar, H. Veisi, S. F. Hojati, H. Salehabadi and R. Nejat Yami, *Chin. Chem. Lett.*, **21**, 1346 (2010).
30. N. Montazeri and S. Mahjoob, S. *Chin. Chem. Lett.*, **23**, 419 (2012).
31. B. Maleki, H. Saleabadi, Z. Sepehr and M. Kermanian, *Coll. Czech. Chem. Commun.*, **76**, 27 (2011).
32. P. V. Shinde, V. B. Labade, J. B. Gujar, B. B. Shingate and M. S. Shingare, *Tetrahedron Lett.*, **53**, 1523 (2012).
33. J. Safari, S. Gandomi-Ravandi and M. Borjeni, *J. Chem. Sci.*, **125**, 1063 (2013).
34. B. Maleki, D. Azarifar, R. Ghorbani-Vaghei, H. Veisi, S. F. Hojati, M. Gholizadeh, H. Saleabadi and M. Khodaverdian-Moghaddam, *Monatsh. Chem.*, **140**, 1485 (2009).
35. H. Veisi and R. Ghorbani-Vaghei, *Tetrahedron*, **66**, 7445 (2010).
36. B. Maleki, R. Tayebee, M. Kermanian and S. Sedigh Ashrafi, *J. Mex. Chem. Soc.*, **57**, 298 (2013).
37. A. Rostami, A. Khazaei, M. Mahboubifar and S. Rahmati, *Org. Prep. Proced. Int.*, **40**, 303 (2008).

38. H. Veisi, M. Amiri, A. H. Hamidian, J. Malakootikhah, L. Fatolahi, A. R. Faraji, A. R. Sedrpoushan, B. Maleki, S. Ghahri Saremi, M. Noroozi, F. Bahadoori and S. Veisi. *Phosphorus, Sulfur, and Silicon*, **185**, 689 (2010).

39. H. Veisi, R. Ghorbani-Vaghei and M. A. Zolfigol, *Org. Prep. Proced. Int.*, **43**, 489 (2011).

40. A. Khazaei and A. Rostami, *Org. Prep. Proced. Int.*, **38**, 484 (2006).

41. S. F. Hojati, B. Maleki and Z. Beykzadeh, *Monatsh. Chem.*, **142**, 87 (2011).

42. D. Azarifar, M. A. Zolfigol and B. Maleki, *Synthesis*, 1744 (**2004**).

43. S. F. Hojati, K. Nikoofar and Z. Etemadifar, *Iran. Chem. Commun.*, **1**, 51 (2013).